WHO guidelines

for plague management:

revised recommendations for the use of rapid diagnostic tests, fluoroquinolones for case management and personal protective equipment for prevention of post-mortem transmission

Web Annex A. Antibiotics for treating plague: a systematic review (executive summary)

Background document for the WHO Plague Guidelines meeting, Madagascar, 20–21 September 2019

Sophie Jullien, Paul Garner

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CHAPTER 1
Background and key questions

Plague is a serious disease and always constitutes a medical emergency, therefore, prompt and appropriate treatment can be life saving. The three main forms of plague have different case-fatality rates:

- bubonic plague is usually transmitted by fleas, and accounts for 80–95% of all cases, with a case-fatality rate of 10–20% *(1)*;
- pneumonic plague is usually transmitted between humans, and is less common, but causes outbreaks with a case-fatality rate that is close to 100% if left untreated and more than 50% even when adequately treated with antimicrobials; and
- systemic plague accounts for 10–20% of cases and can be primary or secondary to bubonic and pneumonic plague.

Streptomycin has been used for the treatment of all three types of plague since 1948. This drug can cure the disease, but has some disadvantages, in that it:

- needs to be given parenterally;
- is not widely available in primary care; and
- has important adverse effects of hearing loss and nephrotoxicity *(2)*.

Other antibiotics have been used in the treatment of these types of plague, but there is a lack of consensus on first-line treatment. The purpose of the WHO Plague Guidelines meeting held in Madagascar from 20 to 21 September 2019 was to formulate recommendations for the use of other antibiotics in the treatment of plague, drawing on multiple sources of evidence.

This review summarizes the evidence that informed the panel discussions during that meeting.

1.1 Scope of the review

The aim of this review is to assess the efficacy and safety of selected antibiotics – aminoglycosides (streptomycin and gentamicin), tetracyclines, fluoroquinolones and chloramphenicol – for the treatment of the different forms of plague in humans.

The review also assesses the efficacy and safety of selected antibiotics used in presumptive treatment of persons who have been in close contact with sick people or contaminated tissues and who are at risk of developing plague. Penicillin, cephalosporins and macrolides were excluded from the review, because they are less effective in the treatment of plague than the antibiotics included in the review.

Given that data are limited, the scope of the review included:

- clinical studies reporting outcomes for plague treatment in adults and children in single cohorts, case series and case reports;
- relevant animal studies;
- recognized adverse effects and their incidence; and
- additional relevant pharmacokinetic data.

The key questions that were addressed are outlined below.

1.2 Pneumonic and septicaemic plague

1.2.1 Treating pneumonic and septicaemic plague

1.2.1.1 Question 1. Are fluoroquinolones as effective as aminoglycosides?

Is monotherapy with a 10–14-day course of an oral fluoroquinolone (ciprofloxacin, levofloxacin, moxifloxacin or ofloxacin) as effective as a 10–14-day course of a parenteral aminoglycoside (streptomycin or gentamicin)?

Streptomycin is the antibiotic of choice for pneumonic and septicaemic plague. However, it has potentially severe adverse effects (ototoxicity and nephrotoxicity), and needs to be administered parenterally (20 intramuscular injections, commonly over a 10-day course). Fluoroquinolones have been proposed as an alternative because they have a good safety profile, can be given orally and are used in the treatment of other lower respiratory tract infections.

1.2.1.2 Question 2. Should fluoroquinolones be added to streptomycin?

Is combination therapy with a 10–14-day course of streptomycin and a fluoroquinolone more effective than monotherapy with a 10–14-day course of streptomycin?

Pneumonic plague is a severe disease with high mortality. A combination therapy might improve outcomes and prevent the development of antimicrobial resistance.

1.2.1.3 Question 3. Are tetracyclines as effective as aminoglycosides?

Is monotherapy with a 10–14-day course of an oral tetracycline (doxycycline) as effective as a 10–14-day course of a parenteral aminoglycoside (streptomycin or gentamicin)?

Doxycycline is bacteriostatic and thus may not be useful in the treatment of pneumonic plague. However, it still appears to be the drug of choice, as per the 2018 recommendations from the United States Centers for Disease Control and Prevention (CDC) (3), and some data have supported its efficacy.

1.2.1.4 Question 4. Is combination therapy with a 2-day course of an aminoglycoside and a 10–14-day course of a tetracycline as effective as monotherapy with a 10–14-day course of an aminoglycoside?

Is combination therapy with a 2-day course of a parenteral aminoglycoside (given at the start of treatment or until 2 days after fever subsides) and a 10–14-day course of an oral tetracycline (doxycycline) as effective as monotherapy with a 10–14-day course of a parenteral aminoglycoside?

Doxycycline is bacteriostatic and can be challenging to administer at the start of treatment for pneumonic plague because patients with the disease tend to have a decreased level of consciousness and may experience vomiting. One way to overcome these potential issues would be to administer a parenteral aminoglycoside with an oral tetracycline for the first 2 days of treatment or until 2 days after fever subsides, to ensure a rapid initial response, and to continue the treatment with an oral tetracycline. This approach would minimize the risk of adverse effects associated with aminoglycosides and avoid the need for injections following the initial treatment, which would allow for early discharge of patients when appropriate.

1.2.2 Postexposure presumptive treatment for pneumonic plague

1.2.2.1 Question 5. Is doxycycline effective for postexposure presumptive treatment?

In people exposed to plague, will a 7-day course of oral doxycycline prevent them developing pneumonic plague?

Doxycycline is bacteriostatic and may not be useful for pneumonic plague. However, it is currently the drug of choice for people who have been exposed to pneumonic plague. If doxycycline is not considered as a drug of choice for treating symptomatic patients with pneumonic plague, should it still be the drug of choice for treating asymptomatic patients potentially infected with an incipient form of the disease?

1.2.2.2 Question 6. Are fluoroquinolones effective for postexposure presumptive treatment?

In people exposed to plague, will a 7-day course of an oral fluoroquinolone prevent them developing pneumonic plague?

Following the previous question, an alternative drug might be considered by the panel as the drug of choice for postexposure presumptive treatment for pneumonic plague.

Fluoroquinolones can be given orally and are safer than tetracyclines in pregnant women and small children. Therefore, it is appropriate to consider the use of a fluoroquinolone for postexposure presumptive treatment of plague.

1.3 Bubonic plague

1.3.1 Treating bubonic plague

1.3.1.1 Question 7. Are tetracyclines as effective as aminoglycosides?

Is monotherapy with a 7-day course of an oral tetracycline (doxycycline) as effective as a 7-day course of a parenteral aminoglycoside (streptomycin or gentamicin) for treating bubonic plague?

Doxycycline is widely accepted as a monotherapy for bubonic plague; however, in some settings, there is concern that a single bacteriostatic drug might not be sufficient, and the preferred option might be treatment with an aminoglycoside or combination treatment.

1.3.1.2 Question 8. Are aminoglycosides combined with tetracyclines as effective as monotherapy?

Is combination therapy with a 7-day course of an aminoglycoside and a tetracycline as effective as monotherapy with a 7-day course of either an aminoglycoside or a tetracycline for treating bubonic plague?

See Question 7.

1.3.2 Postexposure presumptive treatment of bubonic plague

1.3.2.1 Question 9. Is doxycycline effective for postexposure presumptive treatment?

In people exposed to plague, will a 7-day course of oral doxycycline prevent them developing the bubonic form of the disease?

1.3.2.2 Question 10. Are fluoroquinolones effective for postexposure presumptive treatment?

In people exposed to plague, will a 7-day course of an oral fluoroquinolone prevent them developing the bubonic form of the disease?

1.4 Plague meningitis

1.4.1 Treating plague meningitis

1.4.1.1 Question 11. Are fluoroquinolones as effective as chloramphenicol?

Is monotherapy with a 10–14-day course of a fluoroquinolone (ciprofloxacin, levofloxacin, moxifloxacin or ofloxacin) as effective as a 10–14-day course of chloramphenicol for treating plague meningitis?

Chloramphenicol is often used for plague with meningeal involvement, because of its ability to cross the blood–brain barrier. However, it has potentially severe adverse effects. The use of chloramphenicol for treating plague meningitis was clear when the drug of choice for the other *forms of plague was an aminoglycoside; however, because aminoglycosides have poor penetration of the cerebrospinal fluid (CSF), the panel might need to reconsider whether a fluoroquinolone should be the drug of choice for plague meningitis.*

CHAPTER 2
Evidence

2.1 Human studies

2.1.1 Methods

The findings of an extensive systematic review conducted by CDC were assessed *(4,5)*. This section describes the methodology used for the systematic review.

2.1.1.1 Criteria for considering studies for this review

Type of studies

The human studies considered included all types of study that reported the use of at least one antibiotic for the treatment of plague and provided individual-level data.

Participants

Participants were adults and children with plague; pregnant women were excluded. In this review, a confirmed case of plague was defined when *Yersinia pestis* was identified by isolation and phage lysis, or when there was a fourfold change in antibody titre. A probable case of plague was considered when *Y. pestis* was identified – for example, by polymerase chain reaction (PCR) or direct immunofluorescence assay (DFA), or when there was a single positive titre and a suspect case of plague was defined as clinically compatible.

Intervention

The interventions considered were streptomycin, gentamicin, doxycycline, fluoroquinolones or chloramphenicol given as treatment for plague. Cases were excluded when the antibiotic was given as a prophylactic.

Outcomes

Primary

The primary outcome was mortality.

Secondary

Secondary outcomes were:

- time to defervescence;
- secondary forms of plague (e.g. primary bubonic plague that progressed to secondary pneumonic plague or meningitis);
- length of hospital stay;
- other expected adverse outcomes (e.g. necrosis of the extremities or renal failure); and
- intubation or shock.

2.1.1.2 Search methods for identification of the studies

The search strategy is described in Appendix 1.

2.1.1.3 Data collection and analysis

The review authors from the CDC project developed and piloted a data abstraction tool in Microsoft Access. For each study that was included, data were extracted by one person and reviewed by a second person.

The CDC review authors performed data analyses using SAS 9.4.

2.1.1.4 Subgroup analysis

Whenever possible, the potential modifiers were explored by assessing data in different subgroups of patients, including the following.

- Forms of plague: bubonic, septicaemic and pneumonic plague (disaggregated data by antibiotics for plague meningitis were not available).
- Age group: adults and children.
- Initiation of treatment: whether treatment started within the first 2 days of the appearance of symptoms or later.
- Monotherapy and combination therapy.

None of the included studies had disaggregated data on the certainty of diagnosis, i.e. confirmed versus probable or presumptive plague, thus it was not possible to examine this aspect.

2.1.1.5 Assessment of the risk of bias

The CDC team used the modified Newcastle–Ottawa scale to assess the risk of bias. A score was calculated based on the following criteria: laboratory confirmation, representation of plague, antibiotic dosage and timing, pre-existing conditions, mortality and other outcomes. The risk of bias was graded as “not serious”, “serious” or “very serious”, but the details of the scoring system used by the CDC team were not available, which made it difficult to assess the meaning of the risk of bias being “not serious” in terms of establishing the relationship between a drug and an outcome.

2.1.1.6 Data synthesis

It was not possible to perform a quantitative analysis for direct comparison of efficacy between antibiotics, owing to the design of the included studies (which were mostly single cohort studies and case reports) and the heterogeneity of the data. Instead, the findings for each antibiotic are presented in tables and described in the text.

The data are based on case reports and case series from real case scenarios, and most patients received treatment with several antibiotics for different durations. Patients reported as having received monotherapy with an antibiotic did not receive any other antibiotic classified as being of "high efficacy" (e.g. aminoglycosides, tetracyclines, fluoroquinolones and sulfonamides). However, they may have received another antibiotic classified as being of "low efficacy" (e.g. penicillin, cephalosporins and macrolides). Similarly, when an outcome is reported for a combination of two antibiotics, this excludes the use of any other "high-efficacy" antibiotic, but does not exclude the use of any other "low-efficacy" antibiotic.

2.1.2 Results

2.1.2.1 Sources of data

The literature search was conducted by the CDC team and it returned 4874 manuscripts up to 1 August 2019. After screening titles and abstracts, the team retrieved 423 full-text manuscripts, which were assessed against the eligibility criteria. A total of 273 articles that included 723 cases met the inclusion criteria and were included in the systematic review.

Setting and date

A total of 723 cases were described in the literature from 1937 to 2016, from the United States of America (USA) (155; 21%), India (91; 13%), China (80; 11%), Viet Nam (72; 10%), Madagascar (69; 10%), Argentina (53; 7%) and other countries (203; 28%).

Gender and age

Among the 723 cases, 374 (52%) were male and the median age was 22 years (range: 8 days to 80 years).

Clinical types of plague and diagnosis

Among the 723 cases, 64% were classified as bubonic plague, 21% as pneumonic plague, 4% as septicaemic plague, 2% as plague meningitis, 2% as pharyngeal plague and 7% as another form of plague. These proportions were similar in both confirmed cases and probable cases of plague. There were 21% confirmed cases, 36% probable cases and 11% suspected cases of plague. Laboratory testing was not done or was missing in 28% of cases, and was negative in 5% of cases (figures may not add up to 100% due to rounding).

2.1.2.2 Risk of bias

Among the 723 cases assessed by the CDC team, 35 (5%) were classified as having no serious risk of bias, 292 (40%) as having a serious risk of bias and 397 (55%) as having a very serious risk of bias.

2.1.2.3 Effects of intervention

Although we aimed to look at secondary outcomes, we had access to data on only the primary outcome of mortality. The CDC database may have information on other outcomes.

Overall mortality

Overall, the CDC team reported that 152 (21%) of all treated cases (considering all antibiotics) died, with no obvious difference between confirmed and probable cases.

The CDC team also reported that the CFR was higher in cases of septicaemic plague (45%) and plague meningitis (36%), followed by those affected by pneumonic (29%) and bubonic (17%) plague.

Mortality by antibiotic received

The mortality by antibiotic received was as follows.

In patients who received gentamicin (monotherapy or combined therapy), the mortality was 20% (*N*=88).

In patients who received chloramphenicol (monotherapy or combined therapy), the mortality was 15% (*N*=97).

In patients who received a fluoroquinolone (monotherapy or combined therapy), the mortality was 15% (*N*=46).

In patients who received streptomycin (monotherapy or combined therapy), the mortality was 12% (*N*=313).

In patients who received a tetracycline (monotherapy or combined therapy), the mortality was 11% (*N*=149).

Findings on mortality by subgroups – including forms of plague, age group, treatment initiation (within 2 days of symptoms), monotherapy and combined therapy – are given for each antibiotic in Tables 1 and 2.

Table 1. Mortality in humans according to antibiotics received: description of case mix[a]

	Streptomycin	Gentamicin	Tetracyclines Doxycycline	Fluoroquinolones Ciprofloxacin	Chloramphenicol
Number of participants	313	88	149 22	46 29	97
Children: *n* (%)	101 (32%)	32 (36%)	52 (35%) 3 (14%)	8 (17%) 8 (28%)	37 (38%)
Pneumonic and septicaemic plague: *n* (%)	92 (29%)	27 (31%)	29 (19%) 6 (27%)	29 (63%) 13 (45%)	38 (39%)
Treatment initiated within 2 days: *n* (%)	86 (27%)	20 (23%)	41 (28%) 5 (23%)	13 (28%) 8 (28%)	23 (24%)

[a]In columns 4 and 5, the first row includes the results for the drug class, and the second row the results for the specific drug (doxycycline and ciprofloxacin).

Table 2. Mortality in humans according to antibiotics received: results[a]

CFR	Forms of plague	Streptomycin	Gentamicin	Tetracyclines Doxycycline	Fluoroquinolones Ciprofloxacin	Chloramphenicol
Overall CFR	All forms	37/313 (12%)	18/88 (20%)	16/149 (11%) 3/22 (14%)	7/46 (15%) 3/29 (10%)	15/97 (15%)
	PP, SP	14/92 (15%)	9/27 (33%)	7/29 (24%) 1/6 (17%)	7/29 (24%) 3/13 (23%)	7/38 (18%)
	BP	20/204 (10%)	6/29 (21%)	9/110 (8%) 2/16 (13%)	0/15 (0%) 0/14 (0%)	6/48 (13%)
Adults	All forms	24/193 (12%)	11/41 (27%)	10/92 (11%) 2/15 (13%)	7/38 (18%) 3/21 (14%)	10/49 (20%)
	PP, SP	12/68 (18%)	6/22 (27%)	5/25 (20%) 1/6 (17%)	7/28 (25%) 3/12 (25%)	5/23 (22%)
	BP	12/119 (10%)	5/18 (28%)	5/62 (8%) 1/9 (11%)	0/9 (0%) 0/8 (0%)	5/24 (21%)
Children	All forms	10/101 (10%)	6/32 (19%)	4/52 (8%) 0/3 (0%)	0/8 (0%) 0/8 (0%)	4/37 (11%)
	PP, SP	1/10 (10%)	3/5 (60%)	2/4 (50%) None	0/1 (0%) 0/1 (0%)	1/4 (25%)
	BP	6/80 (8%)	0/7 (0%)	2/43 (5%) 0/3 (0%)	0/6 (0%) 0/6 (0%)	1/24 (4%)
Treatment initiated within 2 days	All forms	4/86 (5%)	6/20 (30%)	5/41 (12%) 1/5 (20%)	1/13 (8%) 1/8 (13%)	3/23 (11%)
	PP, SP	2/26 (8%)	5/16 (31%)	2/12 (17%) 0/2 (0%)	1/7 (14%) 1/2 (50%)	2/15 (13%)
	BP	2/57 (4%)	1/4 (25%)	3/28 (11%) 1/3 (33%)	0/6 (0%) 0/6 (0%)	1/7 (14%)
Monotherapy	All forms	14/101 (14%)	7/46 (15%)	5/40 (13%) 0/4 (0%)	1/16 (6%) 0/12 (0%)	5/20 (25%)
	PP, SP	3/31 (10%)	3/8 (38%)	3/8 (38%) 0/1 (0%)	1/6 (17%) 0/2 (0%)	4/13 (31%)
	BP	10/62 (16%)	1/8 (13%)	2/30 (7%) 0/3 (0%)	0/9 (0%) 0/9 (0%)	1/6 (17%)
Monotherapy initiated within 2 days	All forms	2/45 (4%)	2/5 (40%)	1/13 (8%) None	0/7 (0%) 0/6 (0%)	2/8 (25%)
	PP, SP	1/15 (7%)	2/4 (50%)	0/3 (0%) None	0/2 (0%) 0/1 (0%)	2/8 (25%)
	BP	1/27 (4%)	0/1 (0%)	1/9 (11%) None	0/5 (0%) 0/5 (0%)	None
+ Aminoglycosides	All forms	3/7 (43%)	3/6 (50%)	8/71 (11%) 3/10 (30%)	4/17 (24%) 3/12 (25%)	5/38 (13%)
	PP, SP	3/4 (75%)	3/4 (75%)	4/14 (29%) 1/2 (50%)	4/14 (29%) 3/10 (30%)	1/18 (6%)
	BP	0/3 (0%)	0/2 (0%)	4/53 (8%) 2/8 (25%)	0/3 (0%) 0/2 (0%)	4/19 (21%)
+ Doxycycline	All forms	1/2 (50%)	2/8 (25%)	None NA	0/1 (0%) 0/1 (0%)	0/1 (0%)
	PP, SP	1/1 (100%)	0/1 (0%)	None NA	None None	0/1 (0%)
	BP	0/1 (0%)	2/7 (29%)	None NA	0/1 (0%) 0/1 (0%)	None

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CFR	Forms of plague	Streptomycin	Gentamicin	Tetracyclines Doxycycline	Fluoroquinolones Ciprofloxacin	Chloramphenicol
+ Fluoroquinolones	All forms	2/12 (17%)	1/4 (25%)	0/1 (0%) 0/1 (0%)	NA None	None
	PP, SP	2/10 (20%)	1/3 (33%)	None None	NA None	None
	BP	0/2 (0%)	0/1 (0%)	0/1 (0%) 0/1 (0%)	NA None	None
+ Chloramphenicol	All forms	4/34 (12%)	1/3 (33%)	0/6 (0%) 0/1 (0%)	None None	NA
	PP, SP	1/16 (6%)	0/2 (0%)	0/1 (0%) 0/1 (0%)	None None	NA
	BP	3/18 (17%)	1/1 (100%)	0/2 (0%) None	None None	NA

BP: bubonic plague; CFR: case-fatality rate; NA: not applicable; PP: pneumonic plague; SP: septicaemic plague.
[a]In columns 4 and 5, the first row includes the results for the drug class, and the second row the results for the specific drug (doxycycline and ciprofloxacin).

2.2 Animal studies

2.2.1 Methods

2.2.1.1 Criteria for considering studies for this review

We attempted to identify all studies that assessed the efficacy of antibiotic treatment for plague in monkeys or in rodents, and included only these studies using one antibiotic (monotherapy) and reporting mortality or survival as the outcome.

2.2.1.2 Search methods for identification of the studies

We did not impose a language restriction for including studies on monkeys, but we included only studies on rodents published in English, owing to time constraints. We conducted the search through PubMed and contacted experts on this topic to identify unpublished data. The search strategy is described in Appendix 1.

2.2.1.3 Data collection and analysis

One review author assessed the studies for eligibility and extracted data. Quantitative analysis was not performed because of the heterogeneity of the studies; instead, the findings are presented in tables and described in the text.

2.2.1.4 Subgroup analysis

We present the findings under the following subgroups: type of animal models (monkeys and rodents), forms of plague and time of treatment initiation.

2.2.1.5 Assessment of risk of bias

We assessed the design quality, reporting and risk of bias of included studies on monkeys, based on criteria used by other systematic reviews of animal studies including macaques *(6)*. These criteria were based on the Animal Research: Reporting In Vivo Experiments (ARRIVE) guidelines, combined with the findings from a survey assessing the quality of experimental design, statistical analysis and reporting of research using animals *(7,8)*. For each included study, we looked at whether statistical power and sample size calculations were reported, whether the number of animals included in the trial was clearly described, and whether authors declared any conflicts of interest. We also assessed the randomization of animals to intervention groups, baseline characteristics of animals between groups and blinding of the outcome assessors to the allocated group.

Owing to time constraints, we did not assess the risk of bias for the rodent studies.

2.2.1.6 Data synthesis

We summarized the findings separately for the monkey and rodent models.

2.2.2 Results (1): monkeys

The literature search was conducted on 24 June 2019 and it returned four manuscripts that were eligible for inclusion *(9–12)*. In our review we included two additional studies identified by contacting experts *(13,14)*; these studies had not been published, but data were retrieved from reports from the United States Food and Drug Administration (FDA) reports (derived from the technical information provided when the drug was approved by FDA). In addition to those six studies, we included findings from three trials conducted in monkeys that are unpublished but were presented in a brief form by CDC in 2019.1

Details of the characteristics of each study are given in Appendix 2.

2.2.2.1 Description of studies

Type of studies

Four of the included studies were randomized placebo-controlled trials; the other two studies compared the efficacy of several antibiotics but it was unclear whether they had used randomization or which method had been used.

Participants and clinical form of plague

Among the six studies looking at antibiotic efficacy for plague in monkeys, four were conducted in African green monkeys, which are recognized as a rigorous animal model for antibiotic efficacy studies *(15)*, and two were conducted in baboons. From the unpublished findings presented by CDC, two were conducted in African green monkeys, and the third did not report on the species used. Most studies looked at treatment efficacy among monkeys exposed to pneumonic plague with a challenge dose of aerosolized *Y. pestis*, while one study looked at treatment efficacy in monkeys exposed to bubonic plague by subcutaneous administration of *Y. pestis*.

[1] Data presented at the Expert forum on antibiotic treatment and prophylaxis of plague, CDC, Atlanta, May 2019.

Intervention

Four studies evaluated the efficacy of a single antibiotic for treating pneumonic plague: three studies used a fluoroquinolone (levofloxacin, ciprofloxacin or moxifloxacin) for 10 days, and the fourth study used different doses of a next-generation aminoglycoside (plazomicin) for 5 or 10 days. Antibiotic treatment was initiated within 6 hours of the onset of fever for these four studies and in one of the additional data sets *(16)*. The remaining two studies looked at the efficacy of multiple antibiotics used in monotherapy for pneumonic plague (one study) or bubonic plague (one study), initiated immediately or within 48 hours of the onset of fever, and administered for 5–7 days. In the unpublished trials presented by CDC, one trial assessed the efficacy of gentamicin, and two other trials assessed the efficacy of oral and intravenous doxycycline administered for 10 days.

Outcome

The four studies that evaluated the efficacy of a single antibiotic looked at mortality/survival at 28–30 days post-exposure. In the remaining two studies, mortality/survival was reported at 96 hours after treatment initiation in one study, and presumably (not specified) at the end of the 5–7 days of treatment in the other study.

2.2.2.2 Risk of bias

Our findings on the quality of the studies are summarized in Table 3. There were insufficient data to assess the risk of bias in the unpublished findings from CDC.

The results of one of the studies were surprising because there were no deaths among monkeys with pneumonic plague treated with a low-efficacy antibiotic *(11)*. However, we were unable to contact the authors to clarify the integrity of the methods used.

None of the included studies reported a sample size or statistical power calculations. All studies clearly stated the number of animals used in their experiments. Only one study included a conflict-of-interest statement, declaring that none of the authors had competing interests. Four studies were described as randomized trials; however, two did not report using randomization methods, while in one study the method was unclear. Randomization was not mentioned in the remaining two studies. All studies provided basic baseline characteristics; however, in all but one study these were not reported by cohorts (monkeys receiving the intervention versus monkeys receiving placebo). Two studies mentioned blinding methods and one mentioned the absence of blinding; blinding was not reported in the remaining three studies. Although mortality is, overall, an objective outcome, this might apply slightly differently in animals that are subject to euthanasia criteria.

Table 3. **Summary of the quality of studies conducted in monkeys**

Criteria	Mega 2016 *(9)*	Layton 2011 *(10)*	USAMRIID 2012 *(13)*	FDA 2015 *(14)*	Romanov 2001 *(11)*	Romanov 2001 *(12)*
Were sample size and statistical power calculations given?	No	No	No	No	No	No
Was the number of animals included in experiments clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes

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Criteria	Mega 2016 *(9)*	Layton 2011 *(10)*	USAMRIID 2012 *(13)*	FDA 2015 *(14)*	Romanov 2001 *(11)*	Romanov 2001 *(12)*
Were competing interests declared?	No COI statement	Contains COI statement, declaring no COI	No COI statement	No COI statement	No COI statement	No COI statement
Was there randomization?	Yes (computerized system with random number generator)	Unclear[a]	Yes, but methods of randomization not reported	Yes, but methods of randomization not reported	Not reported	Not reported
Was there baseline comparability?	All African green monkeys with at least 2 males and 2 females per cohort	All 3–8 kg African green monkeys aged 2 years and older	All 3–6 kg African green monkeys, 50% males and 50% females	All African green monkeys, 50% males and 50% females	19 baboons: males and females, 3.8–12 kg; 49 baboons: not reported	All 4.1–5.6 kg baboons, males and females
Was the outcome assessor blinded?	Not reported, but objective outcome (death or euthanasia)	Yes	Not blinded	Unclear,[b] but objective outcome	Not reported	Not reported

COI: conflicts of interest; FDA: United States Food and Drug Administration; USAMRIID: United States Army Medical Research Institute of Infectious Diseases.
[a]This was a randomized, placebo-controlled trial. Randomization was done using a computerized number generator. It was unclear whether the three cohorts receiving different doses of exposure were randomized, or whether the attribution of placebo versus intervention was randomized.
[b]Described as a blinded study, but the study does not specify who was blinded.

2.2.2.3 Effects of intervention

The main findings on the effects of the intervention are summarized in Table 4.

Pneumonic plague

All animals (*n*=31) in the placebo group died in the four randomized placebo-controlled trials that evaluated antibiotic efficacy for the treatment of pneumonic plague.

Two of the 37 animals tested in the fluoroquinolone group died. One animal (1/17; 6%) treated with levofloxacin died, but this was attributed to a gastric complication and not to treatment failure. Another animal (1/10; 10%) treated with ciprofloxacin died, with a catheter failure leading to an incorrect administration of the drug to the animal. In the third study assessing treatment with a fluoroquinolone, none of the animals treated with moxifloxacin died.

Of the 52 monkeys treated with plazomicin (a next-generation aminoglycoside), 16 (30.7%) died. However, of those that completed the 10-day treatment course, only one animal (1/12; 8.3%) died in the higher-dose group (there was a potential delay in treatment initiation in this case because of a temperature probe failure), none (0/6) died in the medium-dose group, and one (1/6; 16.7%) died in the lower-dose group.

Two sets of experiments were reported in a fifth study; they showed that all the animals (*n*=62) that received any of the antibiotics tested had survived. Survival was only reported at 96 hours after treatment initiation. The antibiotics that were tested and included in this review were streptomycin (*n*=11), amikacin (*n*=8), tetracycline (*n*=5), ciprofloxacin (*n*=7) and ofloxacin (*n*=7).

Two cohorts of 10 animals each that received gentamicin presented a mortality of 20% and 40%, as reported in the unpublished data reported by CDC.

Two additional cohorts of 10 monkeys were treated with doxycycline and presented a high mortality (60% and 100%), as reported in the CDC unpublished data.

Overall, mortality was low among monkeys treated with any fluoroquinolone or plazomicin for 10 days, and high among monkeys treated with doxycycline.

Bubonic plague

One study assessed different antibiotic monotherapy regimens in 12 cohorts of four monkeys each. The four monkeys that did not receive any antibiotics died, whereas all monkeys receiving an antibiotic survived. The antibiotics tested were intramuscular streptomycin, kanamycin, amikacin, netilmicin or tetracycline, or oral doxycycline, ofloxacin or ciprofloxacin (here, we report only the findings for antibiotics included in our review). In each cohort, treatment started immediately after the onset of fever, inguinal adenopathy or erythema at the inoculation site.

Although all the monkeys died in the placebo group, no monkeys died in any of the groups receiving any antibiotic, including those receiving low-efficacy antibiotics for 5 days. This result is surprising, but we were unable to contact the authors to clarify the integrity of the methods.

Table 4. Summary of studies conducted in monkeys

Study ID and source	Animal model	Animal challenge	Antibiotic tested	Mortality in placebo group	Mortality in intervention group
USAMRIID (unpublished) CDC[a]	Unknown	PP	Gentamicin, IV	Unknown	2/10 (20%) 4/10 (40%)
Mega 2016 *(9)* Literature search	African green monkeys	PP	Plazomicin, IV, for 5 or 10 days	12/12 (100%)	25 mg/kg per day for 5 days: 5/16 (31.3%) 12.5 mg/kg per day for 5 days: 4/6 (66.7%) 6.25 mg/kg per day for 5 days: 5/6 (83.3%) 25 mg/kg per day for 10 days: 1/12 (8.3%) 12.5 mg/kg per day for 10 days: 0/6 (0%) 6.25 mg/kg per day for 10 days: 1/6 (16.7%)
Lockman 2010 *(16)* CDC and Layton 2011 *(10)*[a]	African green monkeys	PP	Doxycycline, orally, for 10 days	Unknown	6/10 (60%)
USAMRIID (unpublished) CDC[a]	African green monkeys	PP	Doxycycline, orally or IV, for 10 days	Unknown	orally: 5/5 (100%) IV: 5/5 (100%)
Layton 2011 *(10)* Literature search	African green monkeys	PP	Levofloxacin, IV, for 10 days	7/7 (100%)	1/17 (6%) (gastric complication)
USAMRIID 2012 *(13)* Experts	African green monkeys	PP	Ciprofloxacin, IV, for 10 days	2/2 (100%)	1/10 (10%) (failed catheter)
FDA 2015 *(14)* Experts	African green monkeys	PP	Moxifloxacin, IV, for 10 days	10/10 (100%)	0/10 (0%)

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Study ID and source	Animal model	Animal challenge	Antibiotic tested	Mortality in placebo group	Mortality in intervention group
Romanov 2001 *(11)* Literature search	Baboons	PP	Aminoglycosides, orally or IV, for 5–7 days Tetracyclines, orally or IV, for 5–7 days Fluoroquinolones, orally or IV, for 5–7 days	NA	0/19 (0%) 0/5 (0%) 0/14 (0%)
Romanov 2001 *(12)* Literature search	Baboons	BP	Aminoglycosides, orally or IV, for 5–7 days Tetracyclines, orally or IV, for 5–7 days Fluoroquinolones, orally or IV, for 5–7 days	4/4 (100%)	0/16 (0%) 0/8 (0%) 0/8 (0%)

BP: bubonic plague; CDC: United States Centers for Disease Control and Prevention; CFR: case-fatality rate; FDA: United States Food and Drug Administration; IV: intravenous; NA: not applicable; PP: pneumonic plague; USAMRIID: United States Army Medical Research Institute of Infectious Diseases.

[a]Unpublished data from CDC presentation (Atlanta, 2019).

2.2.3 Results (2): rodents

The literature search was conducted on 24 June 2019 and returned 94 manuscripts on rodents. We excluded 39 studies that were not published in English. Of the 55 manuscripts in English, 12 met the eligibility criteria for inclusion, and no additional studies were identified through other sources. We excluded a study looking at the efficacy of the fluoroquinolones trovafloxacin and grepafloxacin because both were withdrawn from the market due to adverse effects *(17)*. The final review included 11 studies on rodents.

2.2.3.1 Description of studies

Included studies

All 11 included studies assessed the efficacy of antibiotics given immediately or 1 hour after exposure to a challenge dose of *Y. pestis*, or up to 24 hours following that challenge exposure, simulating postexposure presumptive treatment conditions, in pneumonic or septicaemic forms of plague.

Seven studies evaluated mortality when antibiotics were started more than 24 hours post-challenge exposure (mostly ≥36 hours), simulating plague treatment *(18–24)*.

Three studies assessed the efficacy of pre-exposure prophylaxis with doxycycline, ciprofloxacin, gatifloxacin or moxifloxacin *(23–25)*. The characteristics of each study are given in Appendix 2.

2.2.3.2 Effects of intervention

The main findings are summarized in Appendix 3.

Treatment (antibiotics given ≥36 hours post-challenge exposure); seven studies

For gentamicin, all rodents that received subcutaneous treatment died (n=8), and all rodents that received inhaled treatment survived (n=8) *(19)*.

Tetracyclines were assessed in one study *(23)* and all the animals died (n=unknown).

Six studies evaluated the efficacy of fluoroquinolones, including levofloxacin, ciprofloxacin, ofloxacin, moxifloxacin and gatifloxacin. Overall mortality was low (0–10%) among mice treated 36–42 hours post-challenge exposure, but mortality increased drastically (66–100%) when antibiotics were given 48 hours after exposure.

None of the studies assessed the efficacy of chloramphenicol in rodents.

Postexposure presumptive treatment (antibiotics given within 24 hours post-challenge exposure); 11 studies

Overall, mortality rates were low among the mice receiving an aminoglycoside or a fluoroquinolone within the first 18 hours.

Findings for doxycycline were contradictory.

Pre-exposure prophylaxis; three studies

Overall, there was high mortality in rodents that received doxycycline as pre-exposure prophylaxis, and high survival in rodents that received a fluoroquinolone.

2.3 Safety data

Several sources (listed in Appendix 1) provided information on the most common and serious adverse effects associated with each antibiotic included in this review. The list is not exhaustive but does provide information on all common and serious adverse effects.

Table 5 summarizes the findings. Of note is that aminoglycosides (streptomycin and gentamicin) require therapeutic drug monitoring.

Table 5. Summary of the most common and serious adverse effects

Antibiotic	Common adverse effects	Serious adverse effects
Streptomycin	Oedema and angioneurotic oedema CNS effects: dizziness, headache Facial paraesthesia Muscle cramps Visual disturbances Tinnitus Dyspnoea Fever Eosinophilia	Irreversible ototoxicity (vestibular and cochlear) (wide range of incidence, 7–90%) *(26)* Reversible nephrotoxicity (10–20%; higher incidence in critical patients due to affectation of the renal function) Potentiation of myasthenia gravis Teratogenic (irreversible bilateral congenital deafness)
Gentamicin	Oedema CNS effects: dizziness, headache Muscle cramps Visual disturbances Dyspnoea	Ototoxicity (hearing loss and tinnitus) *(26)* Nephrotoxicity Neuromuscular block (muscle paralysis and apnoea) Potentiation of myasthenia gravis

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Antibiotic	Common adverse effects	Serious adverse effects
Tetracyclines	Gastrointestinal symptoms: diarrhoea, nausea, vomiting, anorexia, weight loss, cramps, dysphagia, abdominal pain (1–5%) Photosensitivity, usually mild (unclear incidence) Tooth discoloration Tinnitus Exanthema Urticaria and angioneurotic oedema Oral candidiasis	Gastrointestinal inflammation and ulceration, oesophagitis, pseudomembranous colitis Intracranial hypertension, pseudotumour cerebri (<1%) Hypersensitivity reactions (<1%): exfoliative dermatitis, Stevens–Johnson syndrome Delayed skeletal development in infants
Fluoroquinolones	Gastrointestinal disorders, generally mild: diarrhoea (5%), nausea (7%), vomiting (2%), constipation (3%), abdominal pain (2%), dyspepsia (2%) Photosensitivity (moxifloxacin most associated with phototoxic reaction), rash (2%), pruritus (1%) CNS disorders: dizziness (3%), headache (6%), insomnia (4%), restlessness Dyspnoea (1%) Vaginitis (1%) Hypoglycaemia (more with moxifloxacin) *(27)* The incidences given above correspond to adverse reactions of levofloxacin, from a safety profile in adults based on 29 Phase III trials including 7537 patients.	Tendonitis, tendon rupture: risk increases with age, renal disease, female sex, non-obese *(28)* Peripheral neuropathy QTc prolongation (RR 1.7–3.3, higher with moxifloxacin) *(29)* Torsade de pointes Exacerbation of myasthenia gravis *Clostridium difficile*-associated diarrhoea Severe hepatic disorders, including fulminant hepatitis Seizure risk in susceptible patients (such as those with epilepsy, renal insufficiency or brain injury) (with ciprofloxacin) *(30)* Mental health effects: agitation, nervousness, disorientation, attention disturbances, memory impairment, delirium Aortic rupture (OR 2.71), especially with exposure >14 days *(31)*
Chloramphenicol	CNS effects: confusion, delirium, headache Gastrointestinal effects: diarrhoea, nausea, vomiting Bone marrow suppression Hypersensitivity reaction	Serious and fatal blood dyscrasias: aplastic anaemia, leukopenia, thrombocytopenia, haemolytic anaemia, leukaemia; idiosyncrasy reaction; incidence of 1/40 000 Grey baby syndrome

CNS: central nervous system; OR: odds ratio; RR: relative risk.

2.4 Pharmacology

Table 6 summarizes the basic pharmacological characteristics of each class of antibiotics, including some pharmacokinetic parameters. The main sources used are listed in Appendix 1.

Table 6. Summary of basic clinical pharmacological characteristics

	Aminoglycosides	Tetracyclines	Fluoroquinolones	Chloramphenicol
Mechanism of action	Bactericidal	Bacteriostatic	Bactericidal	Bacteriostatic[a]
Route of administration	IV, IM	Orally, IV	Orally, IV	Orally, IV
Frequency, daily	1 or 2	1–4	1 or 2	4
Oral absorption[b]	Poor	High	Ciprofloxacin: 70% Levofloxacin: 99% Moxifloxacin: 89% Oflofloxacin: 98%	High

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	Aminoglycosides	**Tetracyclines**	**Fluoroquinolones**	**Chloramphenicol**
CSF penetration[c]	Poor (0–30%)	Poor (10–25%)	Ciprofloxacin: 26% Levofloxacin: 30–50% Moxifloxacin: >50% Ofloxacin: >50%	45–89%
Average serum $t_{1/2}$, in hours	2.5 Streptomycin: 1–2 Gentamicin: 4	6–12 Doxycycline: 18	Ciprofloxacin: 4–6.6 Levofloxacin: 7 Moxifloxacin: 10–14 Ofloxacin: 7	4.1
Risk category in pregnancy[d]	D: "evidence of human risk, but benefits may outweigh"	D: "evidence of human risk, but benefits may outweigh"	C: "animal studies show toxicity, human studies inadequate but benefit of use may exceed risk"	C: "animal studies show toxicity, human studies inadequate but benefit of use may exceed risk"

CSF: cerebrospinal fluid; IM: intramuscular; IV: intravenous; $t_{1/2}$: half-life.

[a]Chloramphenicol is a bacteriostatic drug but has bactericidal effects against some pathogens at high concentrations.

[b]Percentage absorbed per oral route under optimal conditions.

[c]CSF levels with inflammation related to blood concentrations.

[d]Risk categories in pregnancy: A: "studies in pregnant women, no risk"; B: "animal studies no risk, but human studies not adequate or animal studies show toxicity, but human studies show no risk"; C: "animal studies show toxicity, human studies inadequate but benefit of use may exceed risk"; D: "evidence of human risk, but benefits may outweigh"; X: "fetal abnormalities in humans, risk > benefit".

CHAPTER 3
Recommendations

Summarized below, for each of the key questions, are the findings from human and animal studies, together with safety data and the main pharmacological characteristics.

3.1 Treating pneumonic and septicaemic plague

3.1.1 Are fluoroquinolones as effective as aminoglycosides?

Is monotherapy with a 10–14-day course of an oral fluoroquinolone (ciprofloxacin, levofloxacin, moxifloxacin or ofloxacin) as effective as a 10–14-day course of a parenteral aminoglycoside (streptomycin or gentamicin)? Table 7 summarizes the findings.

Table 7. Summary of findings for aminoglycosides and fluoroquinolones as monotherapy for pneumonic plague or septicaemic plague

	Aminoglycosides	Fluoroquinolones
Pharmacology	Bactericidal Parenteral administration	Bactericidal Oral or parenteral administration
Safety data	Reversible nephrotoxicity Irreversible ototoxicity	Safer safety profile compared with aminoglycosides
Human studies	RCTs: no trial directly comparing aminoglycosides with fluoroquinolones. Observational studies: cases treated with gentamicin (*n*=8) had higher mortality than cases treated with streptomycin (*n*=31).	Observational studies: no obvious difference in mortality in patients given fluoroquinolones or aminoglycosides (total 45 patients). No data in children.
Animal studies	For gentamicin: mortality of 20% and 40% in monkeys (unpublished data from CDC). For plazomicin: overall mortality was 30.7% (*n*=52); however, mortality was nil or very low among the monkeys that received 10 days of treatment. No relevant data from rodent studies.	Promising results from studies in monkeys and rodents: - among 37 monkeys treated with a fluoroquinolone, two died (cause of death not attributed to treatment failure); - in rodents, early treatment with fluoroquinolone resulted in low mortality (0–10%); delayed treatment after challenge exposure was associated with much higher mortality (66–100%).
Other considerations	Past experience supports streptomycin monotherapy for treatment of PP or SP.	Approved and commonly used worldwide for treatment of lower respiratory tract infections,

CDC: United States Centers for Disease Control and Prevention; PP: pneumonic plague; RCT: randomized controlled trial; SP: septicaemic plague.

Summary of findings

- Fluoroquinolones have fewer adverse effects and are more convenient to administer than aminoglycosides.
- Fluoroquinolones have good efficacy in animal challenge studies.
- Human studies are too limited to be informative.

3.1.2 Should fluoroquinolones be added to streptomycin?

Is combination therapy with a 10–14-day course of streptomycin and a fluoroquinolone more effective than monotherapy with a 10–14-day course of streptomycin? Table 8 summarizes the findings.

Table 8. **Summary of findings for aminoglycosides and fluoroquinolones combined and an aminoglycoside as monotherapy for pneumonic plague or septicaemic plague**

	Streptomycin + fluoroquinolones versus streptomycin
Human studies	RCTs: no trial found. Observational studies: no obvious difference in mortality in patients given streptomycin + fluoroquinolones (2/10) or streptomycin alone (3/31).
Animal studies	No data on combination treatment in monkeys. We did not seek studies in rodents for combination treatment.

RCT: randomized controlled trial.

Summary of findings

Studies are too limited to be informative.

3.1.3 Are tetracyclines as effective as aminoglycosides?

Is monotherapy with a 10–14-day course of an oral tetracycline (doxycycline) as effective as a 10–14-day course of a parenteral aminoglycoside (streptomycin or gentamicin)? Table 9 summarizes the findings.

Table 9. **Summary of findings for aminoglycosides and tetracyclines as monotherapy for pneumonic plague or septicaemic plague**

	Aminoglycosides	Tetracyclines
Pharmacology	Bactericidal Parenteral administration	Bacteriostatic Oral or parenteral administration
Safety data	Reversible nephrotoxicity Irreversible ototoxicity	Oesophagitis, pseudomembranous colitis Intracranial hypertension Hypersensitivity reactions Delayed skeletal development

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	Aminoglycosides	Tetracyclines
Human studies	RCTs: no trial directly comparing aminoglycosides with tetracyclines for pneumonic plague. Observational studies: cases treated with gentamicin (*n*=8) presented higher mortality than cases treated with streptomycin (*n*=31).	Observational studies: no difference in mortality between tetracycline (*n*=8) and gentamicin (*n*=8), but tetracycline may not be as effective as streptomycin (*n*=31). When tetracycline was started within 2 days of symptoms, all survived (*n*=3). CDC provided detailed data for 5 of the 8 cases treated with a tetracycline as monotherapy, from Madagascar (2), Viet Nam (2) and the USA (1), between 1952 and 2015. Four of these 5 cases survived (unpublished data from Nelson et al.).
Animal studies	For gentamicin: mortality of 20% and 40% in monkeys (unpublished data from CDC). For plazomicin: overall mortality was 30.7% (*n*=52). However, mortality was nil or very low among the monkeys that completed 10 days of treatment. No relevant data from rodent studies.	For oral or IV doxycycline for 10 days: high mortality (60–100%) among monkeys (*n*=20). No relevant data from rodent studies.
Other considerations	Historical experience supports good efficacy of streptomycin monotherapy for treating PP or SP.	None

CDC: United States Centers for Disease Control and Prevention; IV: intravenous; PP: pneumonic plague; RCT: randomized controlled trial; SP: septicaemic plague.

Summary of findings

- Tetracyclines are more convenient to administer and may have a safer profile than aminoglycosides.
- Tetracyclines are associated with higher mortality than streptomycin in both human and monkey studies.

3.1.4 Is combination therapy with a 2-day course of an aminoglycoside and a 10–14-day course of a tetracycline as effective as monotherapy with a 10–14-day course of an aminoglycoside?

Is combination therapy with a 2-day course of a parenteral aminoglycoside (given at the start of treatment or until 2 days after fever subsides) combined with a 10–14-day course of an oral tetracycline (doxycycline) as effective as monotherapy with a 10–14-day course with a parenteral aminoglycoside?

The rationale behind associating an aminoglycoside with a tetracycline for the first 2 days of treatment (or until 2 days after fever subsides) is that the bactericidal action of the aminoglycosides could aid a rapid response to treatment and reduce the duration of contagiousness. Table 10 summarizes the findings.

Table 10. **Summary of findings for aminoglycosides and tetracyclines combined compared with an aminoglycoside as monotherapy for pneumonic plague or septicaemic plague**

	Combination therapy (2-day course of an aminoglycoside + a 10–14-day course of a tetracycline) versus monotherapy with an aminoglycoside
Human studies	RCTs: no trial found. Observational studies: - no disaggregated data referring to this particular regimen from the CDC data - no obvious difference in mortality in patients receiving an aminoglycoside plus a tetracycline (*n*=14) or monotherapy with an aminoglycoside (*n*=39).
Animal studies	No data on combination treatment in monkeys. We did not seek studies in rodents for combination treatment.

CDC: United States Centers for Disease Control and Prevention; RCT: randomized controlled trial.

Summary of findings

Studies are too limited to be informative.

3.2 Postexposure presumptive treatment for pneumonic plague

3.2.1 Is doxycycline effective for postexposure presumptive treatment?

In people exposed to plague, will a 7-day course of oral doxycycline prevent them developing pneumonic plague?

Will the panel recommend this drug for postexposure presumptive treatment?

Notes

Doxycycline is currently recommended for people who have been exposed to pneumonic plague.

The panel may want to use the decision made for Recommendation 3 to assess this question and decide on what to recommend.

If the panel does not recommend doxycycline for treating symptomatic patients with pneumonic plague, what is the rationale for recommending doxycycline for people who may be infected but are asymptomatic?

3.2.2 Are fluoroquinolones effective for postexposure presumptive treatment?

In people exposed to plague, will a 7-day course of treatment with an oral fluoroquinolone prevent them developing pneumonic plague?

Will the panel recommend this drug for postexposure presumptive treatment?

Note

The panel may want to use the decision made for Recommendations 1–5 to assess this question and decide on what to recommend.

3.3 Treating bubonic plague

3.3.1 Are tetracyclines as effective as aminoglycosides?

Is monotherapy with a 7-day course of an oral tetracycline (doxycycline) as effective as a 7-day course of a parenteral aminoglycoside (streptomycin, gentamicin) for treating bubonic plague? Table 11 summarizes the findings.

Table 11. Summary of findings for aminoglycosides and tetracyclines as monotherapy for bubonic plague

	Aminoglycosides	**Tetracyclines**
Pharmacology	Bactericidal Parenteral administration	Bacteriostatic Oral or parenteral administration
Safety data	Reversible nephrotoxicity Irreversible ototoxicity	Oesophagitis, pseudomembranous colitis Intracranial hypertension Hypersensitivity reactions Delayed skeletal development
Human studies	RCTs (findings from one RCT conducted in 2002 *(32)*): - both IM gentamicin and oral doxycycline were found to be highly effective with low rates of adverse events; - patients with suspected BP, SP or PP with symptoms for ≤3 days were randomized to either IM gentamicin or oral doxycycline for 7 days; all 65 were patients with BP who presented with fever, except for one patient with SP plus BP and one patient with PP plus BP; - three patients died (gentamicin group: 2/35; doxycycline group: 1/30), in all cases, death was attributed to advanced disease complications at the start of the therapy; - the median time of defervescence was 1 day in both groups; see Appendix 4 for more details. Observational studies: there is no obvious difference in mortality in patients receiving treatment with either a tetracycline or an aminoglycoside (*n*=100).	
Animal studies	All monkeys given a 5–7-day course of either an aminoglycoside or a tetracycline survived at the end of the treatment (*n*=24).	

BP: bubonic plague; IM: intramuscular; PP: pneumonic plague; RCT: randomized controlled trial; SP: septicaemic plague.

Summary of findings

- Tetracyclines are more convenient to give and may have a safer profile than aminoglycosides.
- On the basis of data in humans, tetracyclines and aminoglycosides were equivalent.

3.3.2 Are aminoglycosides combined with tetracyclines as effective as monotherapy (aminoglycosides or tetracyclines)?

Is combination therapy with a 7-day course of an aminoglycoside and a tetracycline as effective as monotherapy with a 7-day course of either an aminoglycoside or a tetracycline for treating bubonic plague? Table 12 summarizes the findings.

Table 12. **Summary of findings for aminoglycosides and tetracyclines combined and as monotherapy for bubonic plague**

	Combination therapy (aminoglycosides plus tetracyclines) versus monotherapy (aminoglycosides or tetracyclines)
Human studies	RCTs: no trial found. Observational studies: no obvious difference in mortality in patients receiving combination treatment with an aminoglycoside and a tetracycline (*n*=53) or monotherapy with either an aminoglycoside (*n*=70) or a tetracycline (*n*=30).
Animal studies	No data on combination treatment in monkeys. We did not seek studies in rodents for combination treatment.

RCT: randomized controlled trial.

Summary of findings

The studies were too limited to be informative.

3.4 Postexposure presumptive treatment for bubonic plague

3.4.1 Is doxycycline effective for postexposure presumptive treatment?

In people exposed to plague, will a 7-day course of oral doxycycline prevent them developing bubonic plague?

Notes

Doxycycline is currently the drug of choice for people who are at risk of developing bubonic plague.

The panel may want to use the decision made for Recommendation 7 to assess this question.

3.4.2 Are fluoroquinolones effective for postexposure presumptive treatment?

In people exposed to plague, will a 7-day course of an oral fluoroquinolone prevent them developing bubonic plague?

3.5 Treating plague meningitis

3.5.1 Are fluoroquinolones as effective as chloramphenicol?

Is monotherapy with a 10–14-day course of a fluoroquinolone (ciprofloxacin, levofloxacin, moxifloxacin or ofloxacin) as effective as a 10–14-day course of chloramphenicol for the treatment of plague meningitis? Table 13 summarizes the findings.

Table 13. Summary of findings for chloramphenicol and fluoroquinolones for the treatment of plague meningitis

	Chloramphenicol	Fluoroquinolones
Pharmacology	Bacteriostatic Oral or parenteral administration Very good CSF penetration	Bactericidal Oral or parenteral administration Good CSF penetration for moxifloxacin and ofloxacin
Safety data	Bone marrow suppression Grey baby syndrome	Safer safety profile compared with chloramphenicol
Human studies	RCTs: no trial directly comparing chloramphenicol with fluoroquinolones. Observational studies: no patients received chloramphenicol or fluoroquinolones as monotherapy for treating plague meningitis.[a]	
Animal studies	No studies of chloramphenicol or floroquinolone monotherapy in monkeys and rodents.	

CSF: cerebrospinal fluid; RCT: randomized controlled trial; SP: septicaemic plague.
[a] These data were provided on 3 September 2019 and are not included in the "Evidence" section above.

Summary of findings

We found no data from human or animal studies.

To be discussed by the Guidelines Development Group panel during the meeting

When a fluoroquinolone is used for the treatment of plague meningitis, what should be the route of administration and dosage?

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Competing interests

Paul Garner directs a research and development programme (funded by UK AID) that aims to increase the number of health sector decisions in low- and middle-income countries based on systematic reviews and reliable evidence.

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Appendix 1. Literature search

Human studies

The literature search was conducted with no language restriction, by looking for any relevant study in the following databases: PubMed Central; MEDLINE (Ovid), 1946 to present; Embase (OVID), 1947 to present; CINAHL (EBSCO), 1982 to present; Cochrane Library; ClinicalTrials.gov; Scopus; DTIC (Defense Technical Information Center); and Global Health (OVID), 1910 to present. The search strategy used was:

- bubonic plague OR sylvatic plague OR pneumonic plague OR septicemic plague OR *Yersinia pestis*
- AND (treating OR treatment*[1] OR therapy OR therapies OR therapeutic* OR antibiotic* OR anti-bacterial* OR antibacterial* OR antiinfective* OR anti-infective* OR drug* OR vaccine* OR immun* OR infection control OR management OR biological ADJ2 OR weapon* OR warfare OR attack OR mass event* OR biodefense OR disaster prepared* OR disaster response OR plan)
- OR gentamicin OR streptomycin OR doxycycline OR tetracycline OR chloramphenicol OR fluoroquinolone or ciprofloxacin or levofloxacin or moxifloxacin OR ampicillin OR amoxicillin OR penicillin OR cefotaxime OR ceftriaxone.

The systematic review author also searched MMWR, WHO and EID archives for relevant papers; conducted a manual inspection of included bibliographies; and consulted plague subject matter experts.

Animal studies

The search strategy shown below was used to identify relevant animal studies.

[1] The asterisk represents a wildcard; it is used to broaden a search by finding words that start with the same letters (e.g. child* finds "child" and "children").

Search strategy for identification of studies in monkey model	Search strategy for identification of studies in rodent model
- Plague OR *Yersinia pestis* - AND (streptomycin OR gentamicin OR doxycycline OR tetracycline OR chloramphenicol OR fluoroquinolone OR ciprofloxacin OR levofloxacin OR moxifloxacin) - AND monkey*	- Plague OR *Yersinia pestis* - AND (streptomycin OR gentamicin OR doxycycline OR tetracycline OR chloramphenicol OR fluoroquinolone OR ciprofloxacin OR levofloxacin OR moxifloxacin) - AND (rodent* OR mouse OR mice OR rat*)

Safety data

The following sources were used to summarize safety data for each antibiotic:

- Pediamecum, a database on the drugs used most commonly in paediatrics; it was created and is updated by the Committee of Medicines of the Spanish Association of Pediatrics (http://pediamecum.es/) *(1)*;
- material from the FDA Antimicrobial Drugs Advisory Committee meeting held in 2012 (https://wayback.archive-it.org/7993/20170403223651/https:/www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm293600.htm), accessed 1 June 2019; and
- a presentation on “Plague treatment: antibiotic adverse effects for consideration” by Amesh Adalja during the Expert forum on antibiotic treatment and prophylaxis of plague, CDC, Atlanta, May 2019.

Pharmacology

The following sources were used to gather the main characteristics of clinical pharmacology for each antibiotic:

- the *Sanford guide to antimicrobial therapy (2)*;
- a publication by Chopra on tetracyclines *(3)*; and
- Pediamecum *(1)*.

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Appendix 2. Characteristics of included studies

Monkey studies

Table 1. **Characteristics of efficacy studies conducted in monkeys**

Study ID (ref.)	Methods	Findings	Additional details
FDA 2015 *(1)*	This was a randomized, blinded placebo-controlled trial. Participants: 20 African green monkeys (10 males and 10 females). Challenge: pneumonic plague from *Y. pestis* CO92 strain by aerosol exposure. Intervention: - initiated when the animal presented at least 4 hours of sustained fever; - administration: not described; - treatment regimen: moxifloxacin, dose not specified; - placebo: not specified; and - duration of treatment: 10 days.	20 African green monkeys included: 10 received placebo, 10 received levofloxacin. Main outcome measured: survival/death at 30 days after completion of treatment: - placebo group: 10/10 (100%) died between 83 and 139 hours post-treatment; and - moxifloxacin group: 0/10 (0%) died.	Funding: not mentioned. Competing interests: not reported.

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Study ID (ref.)	Methods	Findings	Additional details

Layton 2011 *(2)*	This was a randomized, placebo-controlled trial. Randomization was performed using a computerized system, using a random number generator. It was unclear whether randomization was performed for the three cohorts receiving different doses of exposure, or for attribution of placebo versus intervention.
	Participants:
	- 26 African green monkeys, weight 3–8 kg, aged 2 years and older, with no systemic antibiotics or topical mupirocin ointment received in the 28 days and 14 days before *Y. pestis* challenge exposure, retrospectively;
	- SC implanted telemetry allowing continuous monitoring of body temperature, intrathoracic pressure, respiratory rate, heart rate and electrocardiographic activity; and
	- femoral venous catheter inserted into each participant.
	
	Challenge: pneumonic plague from *Y. pestis* CO92 strain by aerosol exposure. Three cohorts according to the dose of exposure received.
	Intervention:
	- initiated within 6 hours of the onset of fever (≥39 ºC for >1 hour);
	- administration: IV through a 30-minute infusion;
	- treatment regimen: levofloxacin, daily dose of 8 mg/kg followed by 2 mg/kg 12 hours later;
	- placebo: 5% dextrose in water; and
	- duration of treatment: until death/euthanasia or completion of 20 doses of the intervention (10 days).
		26 African green monkeys included: 7 received placebo, 17 received levofloxacin; 2 were removed from analysis (one before and one after *Y. pestis* challenge exposure, due to health reasons for the first case and due to start of treatment before presenting fever for the second case).
		Main outcome measured: survival/death at 28 days post-challenge exposure:
		- placebo group: 7/7 (100%) died/were euthanized before day 5 post-challenge exposure;
		- levofloxacin group: 1/17 (6%) died:
		  - 16 survived with 10 days of treatment until euthanasia on day 28 post-challenge exposure, no evidence of clinical relapse between end of treatment and time of euthanasia; and
		  - 1 case was euthanized on day 9 post-challenge exposure due to a gastric complication (vomiting and inability to retain food); blood culture for *Y. pestis* was positive at the start of the treatment, but negative on days 4–7 and at post-mortem, showing no evidence of treatment failure.
			Conducted at the Lovelace Respiratory Research Institute, Albuquerque (NM), USA.
			Funding: "This project was funded by the National Institute of Allergy and Infectious Diseases, www.niaid.nih.gov, contract N01-AI-4000951. The funding agency's Project Officer approved the study design and manuscript. The Project Officer did not have a role in data collection and analysis, decision to publish, or conclusions."
			Competing interests: "The authors have declared that no competing interests exist."

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Study ID (ref.)	Methods	Findings	Additional details

Mega 2016 *(3)*	This manuscript summarizes the assessment of plazomicin through six cohorts from three studies.
	The total number of African green monkeys were randomized into six exposure cohorts, using a computerized system with a random number generator.
	Participants:
	- 64 African green monkeys (at least 2 males and 2 females per cohort);
	- telemetry implanted within the peritoneum for continuous monitoring of fever, respiratory rate and heart rate; and
	- femoral venous catheter inserted in each participant.
	
	Challenge: pneumonic plague from *Y. pestis* strain Colorado 92 by aerosol exposure, with different exposure doses between the different studies.
	Intervention:
	- initiated within 6 hours of the onset of sustained fever (>39 ºC for 1 hour for the first 2 studies; >1.5 ºC above baseline body temperature for 1 hour for the third study);
	- administration: IV through a 30-minute infusion;
	- treatment regimen: plazomicin, daily dose of 6.25, 12.5 or 25 mg/kg, divided into two doses: 90% of the daily dose followed by 10% 12 hours later;
	- placebo: saline for injection; and
	- duration of treatment: 5 or 10 days, depending on the study cohort.
		64 African green monkeys included across the six cohorts: 12 received placebo, 52 received plazomicin.
		Main outcome measured: survival/ death at 28 to 30 days post-challenge exposure:
		- placebo: 12/12 (100%) died/were euthanized between 71 and 129 hours post-challenge exposure; and
		- intervention group (plazomicin): 16/52 (30.7%) died:
		  - 25 mg/kg per day for 5 days: 5/16 (31.3%) died; two animals succumbed before the end of the 5-day treatment;
		  - 12.5 mg/kg per day for 5 days: 4/6 (66.7%) died; one animal succumbed after receiving all but one treatment doses;
		  - 6.25 mg/kg per day for 5 days: 5/6 (83.3%) died;
		  - 25 mg/kg per day for 10 days: 1/12 (8.3%) died; for the only animal that died in this cohort, the animal's implanted temperature probe failed between time of challenge exposure and treatment and temperature was therefore measured in an alternative way (according to the authors, "this potentially delayed therapy initiation significantly, although it is difficult to know by how long");
		  - 12.5 mg/kg per day for 10 days: 0/6 (0%) died; and
		  - 6.25 mg/kg per day for 10 days: 1/6 (16.7%) died.
		Among the 16 animals treated with plazomicin that died, the cause of death was attributed to meningitis in four cases, and to CNS infection in a fifth case. Among the remaining cases, the cause of death was pneumonia (6), pneumonia/sepsis (1), resurgence of pneumonia (3) and lung damage (1).
			Funding: "Federal funds from the Biomedical Advanced Research and Development Authority, Office of the Assistant Secretary for Preparedness and Response, Office of the Secretary, Department of Health and Human Services, under Contract No. HHSO100201000046C."
			Competing interests: not reported.

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Study ID (ref.)	Methods	Findings	Additional details

Romanov 2001 (PP) *(4)*	This manuscript summarizes the assessment of different antibiotic regimens in eight cohorts of baboons from a first experiment (A). There are no details on randomization or allocation of the monkeys to the different cohorts, and no details on whether investigators were blinded.
	This manuscript also summarizes the findings in a group of baboons infected with plague after starting antibiotic therapy with a group of healthy baboons, to assess contagiousness (B).
	Participants:
	- 19 baboons (males and females), weight 3.8–12 kg for (A); and
	- 49 baboons for (B), including 43 infected and 6 healthy baboons.
	
	Challenge: pneumonic plague from *Y. pestis* 1300 strain by aerosol exposure (1.4×10^4 to 2.8×10^4 live bacteria).
	Intervention:
	- initiated immediately or within 12, 24 or 48 hours of the onset of fever;
	- administration: orally or IM;
	- treatment regimen:
	  - (A): streptomycin 100 mg/day IM, or amikacin 100 mg/day, IM, or tetracycline 100 mg/day, IM, or ceftriaxone 60 mg/day, IM, or doxycycline 32 mg/day, orally, or rifampicin 160 mg/day, orally, or ofloxacin 80 mg/day, orally, or ciprofloxacin 60 mg/day, orally; daily dose divided in two doses and administered every 12 hours;
	  - (B): streptomycin 100 mg/day, IM, or amikacin 100 mg/day, IM, or netilmicin 20 mg/day, IM, or ceftriaxone 60 mg/day, IM, or cefotaxime 60 mg/day, IM, or rifampicin 160 mg/day, orally, or ofloxacin 80 mg/day, orally or ciprofloxacin 60 mg/day, orally; daily dose divided in two doses and administered every 12 hours;
	- control: for (B): six baboons did not receive a challenge dose by aerosol or antibiotics but were exposed to infected baboons; and
	- duration of treatment: 5–7 days.
		(A) 19 baboons included: 8 groups of 2 or 3 baboons, each receiving one of the 8 antibiotics cited under Methods.
		(B) 49 baboons included: 1 group of 8 baboons receiving streptomycin; 7 groups of 5 baboons, each receiving 1 of the remaining 7 antibiotics cited under Methods; 1 group of 6 baboons that did not receive a *Y. pestis* challenge dose and received no antibiotics (control group).
		Main outcome measured:
		- (A): survival/death at 96 hours after starting treatment, and number of bacteria isolated from blood culture and oropharyngeal culture at 0, 12, 24, 36, 48 and 96 hours after starting treatment:
		  - all 19 baboons survived;
		  - from 12 hours onwards, cultures were negative for baboons that received streptomycin, amikacin, ceftriaxone, ofloxacin or ciprofloxacin;
		  - the 2 animals that received tetracycline had a positive oropharyngeal culture at 36 and 48 hours, after negative cultures at 12 and 24 hours, with posterior negative culture at 96 hours;
		  - among the 3 animals that received doxycycline, 1 presented negative cultures from 12 hours; the other 2 animals presented positive oropharyngeal culture at 12 and 24 hours with subsequent negative cultures; and
		  - in the 2 animals that received rifampicin, all cultures were negative from 24 hours onwards.
			Conducted at the Research Institute of Microbiology, Kirov, Russian Federation.
			Funding: Ministry of Defence of the Russian Federation.
			Competing interests: not reported.

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Study ID (ref.)	Methods	Findings	Additional details
Romanov 2001 (BP) *(5)*	This manuscript summarizes the assessment of different antibiotic regimens in 12 cohorts of baboons with no details on randomization or allocation of the baboons to the different cohorts, and no details on whether investigators were blinded. Participants: - 48 baboons (males and females), weight 4.1–5.6 kg. Challenge: bubonic plague from *Y. pestis* 1300 strain by SC administration in a distal extremity. Intervention: - initiated immediately after the onset of fever, inguinal adenopathy or erythema at the inoculation site; - administration: orally or IM; - treatment regimen: streptomycin 100 mg/day, IM, or kanamycin (dosage not reported), IM, or tetracycline 100 mg/day, IM, or amikacin 100 mg/day, IM, or netilmicin 20 mg/day, IM, or ceftizoxime 100 mg/day, IM, or cefotaxime 100 mg/day, IM, or ceftriaxone 60 mg/day, IM, or doxycycline 32 mg/day, orally, or ofloxacin 80 mg/day, orally, or ciprofloxacin 60 mg/day, orally, or rifampicin 160 mg/day, orally; daily dose divided in two doses and administered every 12 hours; - placebo: four baboons did not receive treatment; and - duration of treatment: 5 days for all antibiotics except tetracycline and rifampicin (7 days).	48 baboons included: groups of 4 baboons, each of which received one of the 11 antibiotics cited under Methods except kanamycin (kanamycin is cited in the text but does not appear in the findings); one group of 4 baboons with no antibiotics. Main outcome measured: survival/death (time not specified, probably at the end of the 5- or 7-day treatment): - control group: all 4 baboons that did not receive any antibiotics died; and - all 44 baboons that received any antibiotic survived.	Conducted at the Research Institute of Microbiology, Kirov, Russian Federation. Funding: Ministry of Defence of the Russian Federation. Competing interests: not reported.

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Study ID (ref.)	Methods	Findings	Additional details
USAMRIID 2012, unpublished *(6)*	This was a randomized, placebo-controlled trial, not blinded. Randomization stratified by sex and day of challenge exposure (method used for randomization not provided). Participants: - 12 African green monkeys (6 males and 6 females), weight 3–6 kg; - SC implant for monitoring of body temperature, pulse and pressure every 30 minutes; respiratory rate assessed manually; and - central venous catheter inserted in each participant. Challenge: pneumonic plague from *Y. pestis* CO92 strain by aerosol exposure. Intervention: - treated as a group, initiated when fever for 2 hours in most of the animals (fever defined as >1.5 ºC above baseline body temperature for 2 hours); - administration: IV through a 60-minute infusion; - treatment regimen: ciprofloxacin, 15 mg/kg twice daily; - placebo: not specified; and - duration of treatment: 10 days.	12 African green monkeys included: 2 received placebo, 10 received levofloxacin. Main outcome measured: survival/death at 28 days post-challenge exposure: - placebo group: 2/2 (100%) died at 99 and 98.5 hours post-challenge exposure; and - ciprofloxacin group: 1/10 (10%) died; the animal that succumbed after receiving 8 doses of ciprofloxacin had catheter failure.	Study conducted by the United States Army Medicam Research Institute of Infectious Diseases. Sponsors: FDA/NIAID/USAMRIID Interagency Agreements. Competing interests: not reported.

CNS: central nervous system; FDA: Federal Drug Administration; IM: intramuscular; IV: intravenous; NIAID: National Institute of Allergy and Infectious Diseases; SC: subcutaneous; USAMRIID: United States Army Medical Research Institute of Infectious Diseases; *Y. pestis: Yersinia pestis*.

Rodent studies

Table 2. Characteristics of efficacy studies conducted in rodents

Study ID (ref.)	Drugs tested	Methods	Main findings

Byrne 1998 *(7)*	Streptomycin
	Gentamicin
	Ciprofloxacin
	Ofloxacin
	(Others)
		Animal: female mice.
		Challenge: *Y. pestis* CO92 delivered by aerosol → PP; and SC → BP.
		Intervention: streptomycin, gentamicin (12 or 20 mg/kg), ciprofloxacin, ofloxacin or other antibiotic not addressed in this review, IP, every 6 hours for 5 days:
		- early treatment, initiated 24 hours post-challenge exposure
		- late treatment, initiated 42 hours post-challenge exposure.
		
		Control: normal saline.
		Cohort size: 15–20 (usually 20).
			Main outcome: death/survival up to 14 days after starting treatment:
			- CFR for PP, early treatment:
			  - streptomycin: 0/20 (0%)
			  - gentamicin: 8/40 (20%) for 12 mg/kg dose; 4/20 (20%) for 20 mg/kg dose
			  - ciprofloxacin: 0/35 (0%)
			  - ofloxacin: 0/20 (0%)
			- CFR for PP, late treatment:
			  - streptomycin: 35/85 (41%)
			  - gentamicin: 26/38 (68%) for 12 mg/kg dose; 3/20 (15%) for 20 mg/kg dose
			  - ciprofloxacin: 17/45 (38%)
			  - ofloxacin: 8/20 (40%)
			- CFR for BP treated with streptomycin:
			  - 24 hours post-challenge exposure: 0/20 (0%)
			  - 42 hours post-challenge exposure: 6/20 (30%)
			  - 48 hours post-challenge exposure: 15/20 (75%)
			  - 54 hours post-challenge exposure: 11/20 (55%).

Gur 2018 *(8)*	Gentamicin
	Tobramycin
	(Combinations)
		Animal: female outbred mice.
		Challenge: intranasal fully virulent *Y. pestis* Kimberley53 strain (Kim53) → PP.
		Intervention: initiated 24 and 48 hours post-challenge exposure, for 5 days:
		- gentamicin (3.5 mg/kg per day), by inhalation; or
		- gentamicin (3.5 mg/kg per day), SC; or
		- tobramycin (1.5 mg/kg per day), by inhalation.
		
		Combinations of antibiotics, not summarized for the purpose of this review.
		Control: untreated.
		Cohort size: 8 per cohort.
			Main outcome: death/survival up to 16 days after starting treatment. CFR:
			- when started 24 hours post-challenge exposure, simulating PEPT:
			  - gentamicin, by inhalation: 0/8 (0%); 1/8 (13%) for increased *Y. pestis* infection dose
			  - gentamicin, SC: 5/8 (60%); 6/8 (75%) for increased *Y. pestis* infection dose
			  - tobramycin, by inhalation: 0/8 (0%)
			  - control: 8/8 (100%).
			- when started 48 hours post-challenge exposure:
			  - gentamicin, by inhalation: 0/8 (0%)
			  - gentamicin, SC: 8/8 (100%)
			  - control: 8/8 (100%).

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Study ID (ref.)	Drugs tested	Methods	Main findings
Heine 2007 *(9)*	Gentamicin Doxycycline Levofloxacin	Animal: female BALB/c neutropenic (N) and non-neutropenic (nonN) mice. Challenge: *Y. pestis* CO92 delivered by aerosol → PP. Cohort size: 10 mice. Intervention: levofloxacin (15 mg/kg every 12 hours) or doxycycline (40 mg/kg every 6 hours) or gentamicin (12 mg/kg every 6 hours or 24 mg/kg every 12 hours or 48 mg/kg every 24 hours), IP, initiated 24 hours post-challenge exposure, for 5 days. Control: placebo with saline.	Main outcome: death/survival up to 21 days after starting treatment. CFR: - levofloxacin: nonN 0%; N 0%; control 100% - doxycycline: nonN 10%; N 100%; control 100% - gentamicin: nonN 10% (12 mg/kg every 6 hours), 0% (24 mg/kg every 12 hours) and 20% (48 mg/kg every 24 hours); N 30%, 20% and 20%, respectively; control 100%.
Heine 2014 *(10)*	Ciprofloxacin (Imipenem) (Ceftazidime)	Animal: female BALB/c mice. Challenge: *Y. pestis* CO92 delivered by aerosol → PP. Intervention: ciprofloxacin (30 mg/kg every 12 hours) or imipenem (data not collected for this review) or ceftazidime (data not collected for this review), IP, initiated 24 hours (PEPT experiment) and 42 hours post-challenge exposure (treatment experiment), for 5 days. Cohort size: 10 mice in the ciprofloxacin cohort. Control: 0.85% saline.	Main outcome: death/survival up to 21 days after starting treatment. CFR: - ciprofloxacin as PEPT: 0% - ciprofloxacin as treatment: 50%.

Petersen 2010 *(11)*	Levofloxacin	Animal: Swiss-Webster mice.
		Challenge: *Y. pestis* CO92 by nasal instillation → PP.
		Intervention: levofloxacin at various doses from 0.1 to 15 mg/kg per day, IP, initiated 24, 36 or 48 hours post-challenge exposure for 6 days.
		Control: no antibiotics.
		Cohort size: not reported.
			Main outcome: death/survival at 20 days post-challenge exposure. CFR:
			- when started 24 hours post-challenge exposure:
			  - 5, 10 or 15 mg/kg: 0% died
			  - 1 mg/kg: 20% died
			  - 0.5 or 0.1 mg/kg: 100% died
			- when started 36 hours post-challenge exposure: 5 or 10 mg/kg: 10% died
			- when started 48 hours post-challenge exposure:
			  - 10 mg/kg: 80% died
			  - 5 mg/kg: 90% died

Rahalison 2000 *(12)*	Streptomycin
	Chloramphenicol
		Animal: female OF1 mice.
		Challenge: virulent *Y. pestis* strain 6/69 IV → SP.
		Intervention: initiated 24 hours post-challenge exposure:
		- streptomycin (30 mg/kg every 8 hours), SC, for 2, 3 or 4 days; or
		- chloramphenicol (100 mg/kg every 8 hours), IM, for 2, 3 or 4 days; or
		- OCm (100 mg/kg or 200 mg/kg per dose), IM, as a single injection at 24 hours post-challenge exposure; or
		- OCm (200 mg/kg per dose), IM, as two injections at 24 and 48 hours post-challenge exposure.
		
		Control: physiological saline, IM or SC.
		Cohort size: 5.
			Main outcome: death/survival at 15 days post-challenge exposure. CFR:
			- streptomycin, SC: 1/5 (20%), 0/5 (0%) and 0/5 (0%) after 2, 3 and 4 days of treatment, respectively
			- chloramphenicol, IM: 1/5 (20%) after 4 days of treatment (no results given for 2 and 3 days)
			- OCm, IM, single injection:
			  - 100 mg/kg: 7/10 (70%)
			  - 200 mg/kg: 5/5 (100%)
			- OCm, IM, two injections: 3/5 (60%).

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Study ID (ref.)	Drugs tested	Methods	Main findings

Rosenzweig 2011 *(13)*	Levofloxacin (Cethromycin)	Animal: female Brown Norway rats.
		Challenge: *Y. pestis* CO92 by intranasal inoculation at day 0, and at day 43 or 34 → PP PP.
		Intervention: levofloxacin at various doses from 0.5 to 15 mg/kg per day, IP, or 20 mg/kg per day, orally, initiated 24 hours post-challenge exposure, for 6 days.
		Delayed start at 36, 42 and 48 hours post-challenge exposure with doses of 5 and 10 mg/kg per day, IP, for 6 days.
		Control: phosphate-buffered saline.
		Cohort size: 6 rats per group for treatment started at 24 hours, 9 rats per group for delayed treatment and control.
			Main outcome: death/survival at 42 and 60 days post-challenge exposure for those with antibiotic treatment initiated 24 hours post-challenge exposure; death/survival at 33 and 65 days post-challenge exposure for those with delayed treatment. CFR:
			- when started 24 hours post-challenge exposure:
			  - 15 mg/kg: 0/6 (0%) and 2/6 (33%) at 42 and 60 days, respectively
			  - 10 mg/kg: 0/6 (0%) at 42 and 60 days
			  - 5 mg/kg: 2/6 (33%) at 42 and 60 days
			  - 1 mg/kg: 5/6 (83%) at 42 and 60 days
			  - 0.5 mg/kg: 6/6 (100%) at 42 days
			  - control: 9/9 (100%) at 42 days.
			- CFR for delayed treatment:
			  - at 24, 36 and 42 hours post-challenge exposure, for 10 or 5 mg/kg: 0/9 (0%) at 34 days
			  - at 48 hours post-challenge exposure for 10 or 5 mg/kg: 6/9 (66%) at day 34.

Russell 1996 *(14)*	Doxycycline Ciprofloxacin	Animal: Porton outbred mice. Challenge: IP *Y. pestis* strain GB with 5 or 6 challenge doses → SP. Intervention: - ciprofloxacin, SC, 40 or 20 mg/kg every 12 hours, administered from 48 hours pre-challenge exposure to 5 days post-challenge exposure, or - ciprofloxacin, SC, 40 or 20 mg/kg every 12 hours, initiated 24 hours post-challenge exposure, for 5 days, or - doxycycline, SC, 40 or 20 mg/kg every 12 hours, administered from 48 hours pre-challenge exposure to 4 days post-challenge exposure, or - doxycycline, SC, 40 or 20 mg/kg every 12 hours, initiated 24 hours post-challenge exposure, for 4 days. Control: no antibiotics. Cohort size: 30 mice for each dose cohort of ciprofloxacin, 25 mice for each dose cohort of doxycycline, 10 mice untreated.	Main outcome: death/survival up to 20 days post-challenge exposure. CFR: - ciprofloxacin as pre-exposure prophylaxis: 0/30 (0%) for each dose - ciprofloxacin as PEPT: 14/30 (46.7%) for each dose - doxycycline as pre-exposure prophylaxis: 15/25 (60%) for 40 mg/kg dose, 24/25 (96%) for 20 mg/kg dose - doxycycline as PEPT: 23/25 (92%) for 40 mg/kg dose, 25/25 (100%) for 20 mg/kg dose.

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Study ID (ref.)	Drugs tested	Methods	Main findings
Russell 1998 *(15)*	Doxycycline Ciprofloxacin	Animal: Porton outbred mice. Challenge: *Y. pestis* strain GB and strain CO92 delivered by aerosol → PP. Intervention: ciprofloxacin or doxycycline given at 40 mg/kg every 12 hours, SC, in one of the four regimens: - prophylaxis: administered from 48 hours pre-challenge exposure to 5 days post-challenge exposure - initiated immediately post-challenge exposure, for 5 days - initiated 24 hours post-challenge exposure, for 5 days - initiated 48 hours post-challenge exposure, for 5 days. Control: not specified if placebo or untreated. Cohort size: not reported.	Main outcome: death/survival up to 20 days post-challenge exposure. CFR for both *Y. pestis* strains: - doxycycline 100%; ciprofloxacin 0% - doxycycline 100%; ciprofloxacin 0% - doxycycline 90% and 100% for GB and CO92 strains, respectively; ciprofloxacin 0% - doxycycline 100%; ciprofloxacin 100%. Controls: 100% for all regimens.
Steenbergen 2017 *(16)*	Omadacycline Doxycycline Ciprofloxacin	Animal: female BALB/c mice. Challenge: *Y. pestis* CO92 delivered by aerosol → PP. Intervention: omadacycline (5, 10, 20 or 40 mg/kg every 12 hours) or doxycycline (5, 10, 20 or 40 mg/kg every 12 hours) or ciprofloxacin (15 mg/kg every 12 hours), IP, initiated 1 hour post-challenge exposure, for 7 days. Control: saline (0.2 mL every 12 hours), IP, for 7 days. Cohort size: 10 mice.	Main outcome: death/survival up to 38 to 41 days after starting treatment. CFR: - omadacycline: 10% (40 mg/kg), 0% (other doses) - doxycycline: 10% (40 mg/kg), 0% (other doses) - ciprofloxacin: 0%.

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Study ID (ref.)	Drugs tested	Methods	Main findings

Steward 2004 *(17)*	Ciprofloxacin
	Gatifloxacin
	Moxifloxacin
		Animal: female BALB/c inbred mice.
		Challenge: *Y. pestis* strain GB delivered SC and by aerosol → SP and PP.
		Intervention: ciprofloxacin, gatifloxacin or moxifloxacin: 2 mg every 12 hours, orally, for 7 days:
		- systemic challenge (SP): initiated 1 hour pre-challenge exposure, or 6, 18 or 24 hours post-challenge exposure
		- aerosol challenge (PP): initiated 6, 18, 30 or 48 hours post-challenge exposure.
		
		Control: deionized water.
		Cohort size: 18 mice per cohort; 252 mice for each of infection route.
			Main outcome: death/survival up to 21 days after starting treatment. CFR:
			- systemic challenge (SP):
			  - ciprofloxacin: 1 hour pre-challenge exposure: 0/18 (0%); 6 hours post-challenge exposure: 0/18 (0%); 18 hours post-challenge exposure: 3/18 (17%); 24 hours post-challenge exposure: 13/18 (72%); control: 18/18 (100%)
			  - gatifloxacin: 1 hour pre-challenge exposure: 0/18 (0%); 6 hours post-challenge exposure: 0/18 (0%); 18 hours post-challenge exposure: 2/18 (11%); 24 hours post-challenge exposure: 5/18 (28%); control: 18/18 (100%)
			  - moxifloxacin: 1 hour pre-challenge exposure: 0/18 (0%); 6 hours post-challenge exposure: 0/18 (0%); 18 hours post-challenge exposure: 8/18 (45%); 24 hours post-challenge exposure: 12/18 (67%); control: 18/18 (100%)
			- aerosol challenge (PP):
			  - ciprofloxacin: 6, 18 and 30 hours post-challenge exposure: 0/18 (0%); 48 hours post-challenge exposure: 17/18 (94%); control: 18/18 (100%)
			  - gatifloxacin: 6, 18 and 30 hours post-challenge exposure: 0/18 (0%); 48 hours post-challenge exposure: 12/18 (67%); control: 18/18 (100%)
			  - moxifloxacin: 6, 18 and 30 hours post-challenge exposure: 0/18 (0%) each; 48 hours post-challenge exposure: 10/18 (56%); control: 18/18 (100%).

BP: bubonic plague; CFR: case-fatality rate; IM: intramuscular; IP: intraperitoneal; IV: intravenous; nonN: non-neutropenic; PEPT: postexposure presumptive treatment; PP: pneumonic plague; SC: subcutaneous; SP: systemic plague; *Y. pestis: Yersinia pestis*.

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Appendix 3. Summary of findings from studies conducted in rodents

Tables 1–3 show the mortality reported for treatment (initiated ≥36 hours post-challenge exposure), for postexposure presumptive treatment (initiated at ≤24 hours post-challenge exposure) and for pre-exposure prophylaxis (initiated before challenge), respectively.

Table 1. Mortality reported for treatment (initiated ≥36 hours post-challenge)

Study (ref.)	Aminoglycosides		Tetracyclines	Fluoroquinolones			Chloramphenicol
	Streptomycin	Gentamicin	Doxycycline	Levofloxacin	Ciprofloxacin	Moxifloxacin or ofloxacin	
Byrne 1998 *(1)*	41% (35/85)	68% (26/38)[a] 15% (3/20)[a]	NA	NA	38% (17/45)	Ofloxacin 40% (8/20)	NA
Gur 2018 *(2)*	NA	48 hours: 0% (0/8) (by inhalation); 100% (8/8) (SC)	NA	NA	NA	NA	NA
Heine 2014 *(3)*	NA	NA	NA	NA	42 hours: 50% (5/10)	NA	NA
Petersen 2010 *(4)*	NA	NA	NA	36 hours: 10% (≥5 mg/kg) 48 hours: 80% (10 mg/kg); 90% (5 mg/kg)	NA	NA	NA
Rosenzweig 2011 *(5)*	NA	NA	NA	36 hours: 0% (0/9) (≥5 mg/kg) 42 hours: 0% (0/9) (≥5 mg/kg) 48 hours: 66% (≥5 mg/kg)	NA	NA	NA
Russell 1998 *(6)*	NA	NA	48 hours: 100%	NA	48 hours: 100%	NA	NA
Steward 2004 *(7)*	NA	NA	NA	NA	Pneumonic challenge: 30 hours: 0% (0/18) 48 hours: 94% (17/18)	Pneumonic challenge: Gatifloxacin 30 hours: 0% (0/18) 48 hours: 67% (12/18) Moxifloxacin 30 hours: 0% (0/18) 48 hours: 56% (10/18)	NA

NA: not applicable; SC: subcutaneous.
[a] Case-fatality rate for different ***Y. pestis*** infection doses.

Table 2. **Mortality reported for postexposure presumptive treatment (initiated at ≤24 hours post-challenge exposure)**

Study and source	Aminoglycosides: Streptomycin	Aminoglycosides: Gentamicin[a]	Tetracyclines: Doxycycline	Fluoroquinolones: Levofloxacin	Fluoroquinolones: Ciprofloxacin	Fluoroquinolones: Gatifloxacin or ofloxacin	Chloramphenicol
Byrne 1998 *(1)*	0% (0/20)	20% (8/40)[b] 20% (4/20)[b]	NA	NA	0% (0/35)	Ofloxacin 0% (0/20)	NA
Gur 2018 *(2)*	NA	By inhalation: 0% (0/8); 10%[c] SC: 60% (5/8); 75%[c] Tobramycin By inhalation: 0%	NA	NA	NA	NA	NA
Heine 2007 *(8)*	NA	10%; 0%; 20%[b] Neutropenic: 30%; 20%; 20%[b]	10% Neutropenic 100%	0% Neutropenic 0%	NA	NA	NA
Heine 2014 *(3)*	NA	NA	NA	NA	0% (0/10)	NA	NA
Petersen 2010 *(4)*	NA	NA	NA	0% (≥5 mg/kg) 20% (1 mg/kg) 100% (≤0.5 mg/kg)	NA	NA	NA
Rahalison 2000 *(9)*	20% (1/5) (2 days treatment) 0% (0/5) (3 days) 0% (0/5) (4 days)	NA	NA	NA	NA	NA	IM: 20% (1/5) (4 days treatment) OCm IM, 1 dose: 100% (5/5); 70% (7/10)[d]; 2 doses: 60% (3/5)
Rosenzweig 2011 *(5)*	NA	NA	NA	0% (0/6) (≥10 mg/kg) 33% (2/6) (5 mg/kg) 83% (5/6) (1 mg/kg) 100% (6/6) (0.5 mg/kg)	NA	NA	NA
Russell 1996 *(10)*	NA	NA	92% (23/25) (40 mg/kg) 100% (25/25)(20 mg/kg)	NA	47% (14/30)(40 mg/kg) 47% (14/30)(20 mg/kg)	NA	NA
Russell 1998 *(6)*	NA	NA	100%; 90–100%	NA	0%; 0%	NA	NA
Steenbergen 2017 *(11)*	NA	NA	10% (1/10) (40 mg/kg) 0% (0/10) (≤20 mg/kg)	NA	0% (0/10)	NA	NA

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Study and source	Aminoglycosides		Tetracyclines	Fluoroquinolones			Chloramphenicol
	Streptomycin	Gentamicin[a]	Doxycycline	Levofloxacin	Ciprofloxacin	Gatifloxacin or ofloxacin	
Steward 2004 (*7*)	NA	NA	NA	NA	Systemic challenge: 6 hours: 0% (0/18) 18 hours: 17% (3/18) 24 hours: 72% (13/18) Pneumonic challenge: 6 hours: 0% (0/18) 18 hours: 0% (0/18)	***Gatifloxacin*** Systemic challenge: 6 hours: 0% (0/18) 18 hours: 11% (2/18) 24 hours: 28% (5/18) Pneumonic challenge: 6 hours: 0% (0/18) 18 hours: 0% (0/18) Moxifloxacin Systemic challenge: 6 hours: 0% (0/18) 18 hours: 45% (8/18) 24 hours: 67% (12/18) Pneumonic challenge: 6 hours: 0% (0/18) 18 hours: 0% (0/18)	NA

IM: intramuscular; OCm: oily chloramphenicol; SC: subcutaneous.
[a] Or another aminoglycoside.
[b] Case-fatality rate for the different antibiotic doses.
[c] Case-fatality rate for the different *Y. pestis* infection doses.
[d] A lower *Y. pestis* infection dose was used for this cohort.

Table 3. **Mortality reported for pre-exposure prophylaxis (initiated before challenge)**

	Aminoglycosides		Tetracyclines	Fluoroquinolones			
Study and source	**Streptomycin**	**Gentamicin**	**Doxycycline**	**Levofloxacin**	**Ciprofloxacin**	**Moxifloxacin or ofloxacin**	**Chloramphenicol**
Russell 1996 *(10)*	NA	NA	48 hours pre-challenge exposure: 60% (15/25) for 40 mg/kg per dose regimen 96% (24/25) for 20 mg/kg per dose regimen	NA	48 hours pre-challenge exposure: 0% (0/30)	NA	NA
Russell 1998 *(6)*	NA	NA	48 hours pre-challenge exposure: 100%	NA	48 hours pre-challenge exposure: 0%	NA	NA
Steward 2004 *(7)*	NA	NA	NA	NA	Systemic challenge, 1 hour pre-challenge exposure: 0% (0/18)	Systemic challenge, 1 hour pre-challenge exposure: Gatifloxacin 0% (0/18) Moxifloxacin 0% (0/18)	NA

NA: not applicable.

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Appendix 4. Characteristics of a randomized controlled trial comparing gentamicin and doxycycline

Table 1 shows the results of a randomized controlled trial comparing gentamicin and doxycycline for the treatment of bubonic or systemic plague.

Table 1. Randomized controlled trial comparing gentamicin and doxycycline for treatment of bubonic or systemic plague

Author (ref.)	Methods	Findings	Additional information
Mwengee 2006 *(1)*	Study design: randomized controlled trial. Setting: United Republic of Tanzania, plague-endemic area. Date: January to April 2002. Participants: - *n*=65 - inclusion criteria: persons of all ages and both sexes who presented with ≤3 days of fever and bubo, pneumonia or septicaemia. Interventions: - group A: gentamicin (2.5 mg/kg every 12 hours), IM, for 7 days; - group B: doxycycline (100 mg [adults] and 2.2 mg/kg [children] every 12 hours), orally, for 7 days.	All the patients presented with BP, except for one with SP (1 week after treatment of bubo that resolved) and one with pneumonia and a bubo. Age: 7 months to 65 years. Diagnosis of plague confirmed by culture or serological testing in 89% (gentamicin group) and 84% (doxycycline group). Mortality: - gentamicin: 2/35; - doxycycline: 1/30. These deaths occurred on day 1 and 2 after starting treatment and were attributed to "advanced disease and complications, including pneumonia, septicaemia, haemorrhage, and renal failure at the start of therapy". Relapse: none reported in any group. Time to defervescence, median days (range): - gentamicin: 1 (0–5) - doxycycline: 1 (0–4). Of note, 35/35 in the gentamicin group and 28/30 in the doxycycline group presented with fever. Adverse events: - no significant differences between the gentamicin group (7 cases with any adverse events) and the doxycycline group (2 cases with any adverse events); - serum creatinine concentration after 7 days of treatment was significantly higher in the gentamicin group than in the doxycycline group (mean in mg/dL [SD]: 1.4 [0.44] versus 0.70 [0.18], p<0.05) (mean in mg/dL [SD]: 1.4 [0.44] versus 0.70 [0.18], p<0.05).	Details of the three cases with fatal outcome. - A girl aged 10 years with simultaneous presentation of pneumonia and submandibular bubo, suggesting exposure to an aerosol of *Y. pestis* from another person with pneumonic plague, and suggesting that the inoculum reached the lungs by inhalation at the same time as it reached the submandibular lymph nodes through the oral mucosa. The child developed symptoms 1 day before admission; she received one dose of gentamicin and died 3 hours later. - A 65-year-old woman had painful swelling 7 days before admission. She treated herself with tetracyclines (8 tablets) and the swelling subsided, "but regrowth of residual bacteria in the blood caused fatal septicaemia before the immune response was protective". - A 34-year-old pregnant woman with presumptive bubonic plague died after an abortion, with complications of haemorrhage and renal failure prior to randomization.

BP: bubonic plague; IM: intramuscular; SD: standard deviation; SP: systemic plague.

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